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Antibiotics and antibiotic resistance genes in global lakes: A review and meta-analysis

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Abstract

Lakes are an important source of freshwater, containing nearly 90% of the liquid surface fresh water worldwide. Long retention times in lakes mean pollutants from discharges slowly circulate around the lakes and may lead to high ecological risk for ecosystem and human health. In recent decades, antibiotics and antibiotic resistance genes (ARGs) have been regarded as emerging pollutants. The occurrence and distribution of antibiotics and ARGs in global freshwater lakes are summarized to show the pollution level of antibiotics and ARGs and to identify some of the potential risks to ecosystem and human health. Fifty-seven antibiotics were reported at least once in the studied lakes. Our meta-analysis shows that sulfamethoxazole, sulfamerazine, sulfameter, tetracycline, oxytetracycline, erythromycin, and roxithromycin were found at high concentrations in both lake water and lake sediment. There is no significant difference in the concentration of sulfonamides in lake water from China and that from other countries worldwide; however, there was a significant difference in quinolones. Erythromycin had the lowest predicted hazardous concentration for five percent of the species (HC_5) and the highest ecological risk in lakes. There was no significant difference in the concentration of sulfonamide resistance genes (*sul1* and *sul2*) in lake water and river water. There is surprisingly limited research on the role of aquatic biota in propagation of ARGs in freshwater lakes. As an environment that is susceptible to cumulative build-up of pollutants, lakes provide an important environment to study the fate of antibiotics and transport of ARGs with a broad range of niches including bacterial community, aquatic plants

and animals.

Keywords: species sensitivity distributions; niche; aquatic biota; antibiotics; antibiotic resistance genes; meta-analysis

1. Introduction

The discovery of penicillin by Sir Alexander Fleming in 1928 opened the modern era of antibiotic innovation and development (Fleming 1929). Today, antibiotics are not only used as medicine for humans but are also widely used in animal husbandry and aquaculture. However, antibiotics that are unintentionally discharged into the environment pose a great threat to ecosystems and human health. These antibiotics can accumulate in food webs and, even more alarming, antibiotic resistance genes (ARGs) can be transferred between environmental bacteria and human pathogens (Bengtsson-Palme and Larsson 2015; Du and Liu 2012; Li et al. 2015; Martinez et al. 2015; Van Boeckel et al. 2015). Antibiotic resistance is not a new phenomenon (D'Costa et al. 2011; Wright and Poinar 2012), but the rapid and widespread increase of ARGs has been accelerated in recent years with the increase in discharge of antibiotics and other pollutants (e.g., heavy metals) into the environment (Bengtsson-Palme et al. 2014; Czekalski et al. 2014; Yang et al. 2017b; Yin et al. 2013). In fact, ARGs have recently been regarded as an emerging pollutant (Pruden et al. 2006). As such, antibiotics and their effects on the environment (ARGs, antibiotic resistant bacteria (ARB), etc.) have become an important theme in environmental science.

Aquatic environments are major pools for antibiotics and ARGs. Effluents from wastewater treatment plants, industry, hospitals and pig farms, for example, will all eventually reach some water source (Lavilla Lerma et al. 2014; Liu et al. 2012; Zhang et al. 2009a; Zhu et al. 2013). The effects of antibiotics on aquatic micro-organisms,

62 the nitrogen cycle and natural ecosystems have been summarized (Grenni et al. 2018;
63 Roose-Amsaleg and Laverman 2016; Välitalo et al. 2017). The distribution and
64 environmental behaviour (e.g., adsorption and degradation) of antibiotics in aquatic
65 environments have also been reviewed, (Bu et al. 2013; Kümmerer 2009a; b; Liu and
66 Wong 2013). However, some aquatic environments, specifically lakes and rivers,
67 behave differently due to their different hydraulic characteristics. In rivers, the
68 concentration of pollutants in sediments gradually decreases downstream of a source
69 due to hydraulic characteristics (Pruden et al. 2012; Reuther 2009). Rivers seem to
70 have received most attention among aquatic environments, likely due to their rapid
71 transport of antibiotics and ARGs and the obvious identification of pollution sources
72 and landscapes in different reaches (Chen et al. 2013; Pruden et al. 2012;
73 Rodriguez-Mozaz et al. 2015; Storteboom et al. 2010). In lakes, the residence time of
74 contaminants increases because of the long water retention time relative to rivers.
75 This means that pollutants from discharges slowly circulate around the lakes and
76 makes pollution control in lake basins especially critical (Lyandres 2012; Reuther
77 2009). Due to these characteristics, lakes are predicted to have the potential to store
78 and accumulate ARGs to a greater extent than rivers (Czekalski et al. 2015). Lakes
79 serve as an important drinking source of freshwater, containing nearly 90% of the
80 liquid surface fresh water worldwide; in contrast, rivers contain only 2% (McConnell
81 and Abel 2013).
82 Until now, no comprehensive review of antibiotics and ARGs in lakes has been
83 conducted. In this review, we collated the occurrence, distribution and risk of

antibiotics and ARGs in lakes. The objectives were to (1) identify antibiotics with high concentrations through a meta-analysis and prioritize antibiotics with potential ecological risk in lakes; (2) examine the difference in antibiotic pollution between lakes in China and in other countries worldwide, as well as the temporal trend of antibiotics in the most-studied lake, Taihu Lake; and (3) reveal the ARG pollution status in lakes. Factors influencing ARG propagation, potential risks of ARGs to human health, and the bioaccumulation of antibiotics in lakes were also discussed.

2. Methodology

2.1 Data collection

To survey antibiotics and ARGs in lakes worldwide, we used the Web of Knowledge database (http://apps.webofknowledge.com) to retrieve publications. Our search terms included [lake AND antibiotic] AND/OR [lake OR river AND/OR antibiotic resistance genes] AND/OR [lake OR river AND/OR antimicrobial resistance genes]. The database was searched for studies published up to 18 January 2018. Publications were then checked individually to eliminate any duplicates or irrelevant articles. Ultimately, 45 relevant papers reporting antibiotics in global lakes met our criteria. The name, country, antibiotic and/or ARG concentrations, and sampling dates are provided in Tables S1-S5, Supplementary material I. Seventeen and forty-seven studies respectively reported ARG analysis using culture-independent methods in lakes and rivers (Tables S1-S3, Supplementary material II). Trimethoprim/sulfamethoxazole (TMP/SMX), also known as co-trimoxazole, is used to treat a variety of bacterial infections, and TMP/SMX concentrations were included

with sulfonamides. It should be noted that several anonymous lakes in India that receive effluent from treatment plants had concentrations of quinolone antibiotics at μg L^{-1} or mg L^{-1} levels (Fick et al. 2009), concentrations that are 10^3 to 10^4 times higher than those detected in other lakes (Table S3, Supplementary material I). Therefore, these lakes were not included in the meta-analysis. Toxicology data for antibiotics on aquatic organisms were retrieved from the United States Environmental Protection Agency (USEPA) ECOTOX database (https://cfpub.epa.gov/ecotox/). The search criteria used to gather the appropriate toxicity data included the following: freshwater medium, endpoint of lethal concentration required to kill 50% of the population (LC_{50}) or half maximal effective concentration (EC_{50}), exposure duration of <10 days, and test location of the laboratory. Toxicity data for samples without concentration ranges were not used in this study.

2.2 Statistical analysis

2.2.1 Meta-analysis

The mean concentrations of antibiotics were either provided in the publications or calculated using the original data. Concentrations that were "not detected" or "below detection limit" were entered as zero values, similar to a recent meta-analysis on organic contaminants (Meng et al. 2016). Antibiotic concentrations from the same lake but from different sampling years were considered as different data entries; however, antibiotic concentrations from the same lake but from different seasons in the same year were used to obtain a single mean value. The concentrations of antibiotics in the water and sediment were recorded in ng L^{-1} and ng g^{-1}, respectively.

Only antibiotics with at least two values were included in the meta-analysis. The median values and their confidence intervals for the mean concentrations of antibiotics in lakes across the Earth were calculated with the wilcox.test function in R software (R Foundation for Statistical Computing, Vienna, Austria). Comparisons of the concentrations of antibiotics in lakes from China and other countries worldwide were examined by a Mann-Whitney U test in R software. The temporal trend of antibiotics in Taihu Lake, China was analysed with a Pearson correlation analysis. Mann-Whitney U tests were used to compare the maximum relative abundances of *sul1* and *sul2* between lakes and rivers, and the absolute abundances of *sul1* between lakes and rivers.

2.2.2 Ecological risk assessment of antibiotics

Information on the toxicological impacts of many potentially harmful antibiotics is lacking (Välitalo et al. 2017). Therefore, as shown by Staples et al. (2008), antibiotics that had EC_{50} or LC_{50} data for at least four aquatic species within the ECOTOX database were analysed for species sensitivity distribution (SSD) analysis. The hazardous concentrations for 5% of the species (HC_5) derived from SSD were accompanied by a confidence limit that conveys information about the shape of the statistical distribution of toxicity values and their variance (Belanger et al. 2016). The values of HC_5 for antibiotics were calculated with R software. HC_5 values were then used to calculate the predicted no effect concentrations (PNEC) with an application factor of 5. The ecological risk of antibiotics in lake water was analysed with a hazard quotient (HQ), which is the ratio of the measured environmental concentration (MEC)

150 and PNEC.

151 **3. Antibiotics in lakes**

152 **3.1 Overview of antibiotics detected in global lakes**

153 The detection of antibiotics in lakes began in 2002 in Lake Ontario with the use of
154 liquid chromatography-mass spectrometry (LC-MS) and liquid chromatography
155 fluorescence detection (LC-FLD) (Nakata et al. 2005). Most later studies used the
156 LC/MS/MS system, which is more efficient than only using the parent ions as in
157 LC-MS analysis (Tables S1-S5, Supplementary material I). There were 57 antibiotics
158 reported at least once in the water and sediments (Tables S1-S5, Supplementary
159 material I). Antibiotics detected in lakes were classified into the following categories:
160 sulfonamides, tetracyclines, quinolones, macrolides, lincosamides, and others
161 (β-lactam, quinoxalines, and polyether and amphenicol antibiotics) (Table 1). The
162 detection frequency may be related with the degradation and adsorption behaviour of
163 antibiotics in lake water and sediments. Tetracyclines, fluoroquinolones and
164 macrolides have a strong adsorption on particles and sediments (Huang et al. 2011;
165 Kümmerer 2009a). Partitioning in the sediment could be one of the main reasons for
166 the frequent detection of tetracyclines and fluoroquinolones in Chinese rivers (Zhou et
167 al. 2011). β-Lactam antibiotics are easily hydrolysed in weakly acidic or alkaline
168 conditions (Braschi et al. 2013) and could be effectively removed by ozonation,
169 Fenton/photo-Fenton, or semiconductor photocatalysis (Homem and Santos 2011).
170 For these reasons, β-lactam antibiotics may have a low detectability in some
171 environments. The number of studies and the investigated antibiotics are summarized

172 in Table 1. In general, it can be concluded from Table 1 that (1) sulfonamides and
173 quinolones are the most commonly investigated groups in lakes worldwide; (2)
174 sulfonamides and tetracycline antibiotics are only found in lake sediments from China;
175 (3) water was the main target for antibiotic analysis in freshwater lakes, rather than
176 sediment; (4) China was the primary country for the studies on lake antibiotics,
177 although 11 other countries also had studies (including Switzerland, Sweden, Turkey,
178 Greece, Germany, Spain, Italy, the United States of America, Canada, India, and
179 Bolivia) (Fig. S1 in Supplementary material I). No reports about antibiotics in lakes
180 were recorded in Africa and Oceania, which are needed in further studies to
181 understand the antibiotic pollution status in lakes worldwide.

182 **3.2 Levels of antibiotics in the water and sediments of global lakes**

183 **3.2.1 Antibiotics in the bulk water of lakes**

184 The average concentrations of 40 antibiotics in lake waters across the globe were
185 retrieved, and the median concentration value and confidence intervals were
186 calculated for each antibiotic (Fig. 1). Seven of the antibiotics had median values that
187 were less than 1 ng L^{-1} or at the ppt level, including sulfapyridine, sulfathiazole,
188 lomefloxacin, danofloxacin, marbofloxacin, josamycin, and spiramycin. The median
189 values for thirteen of the antibiotics were between 1 and 10 ng L^{-1}, including 5
190 sulfonamides, 1 tetracycline, 4 quinolones, 2 macrolides, and 1 lincosamide. Twenty
191 of the antibiotics had median concentrations that were above 10 ng L^{-1}, including 6
192 sulfonamides and trimethoprim, 3 tetracyclines, 3 quinolones, 5 macrolides and
193 lincosamides, and 2 other antibiotics.

194 *Sulfonamides*

195 Sulfamethoxazole (SMX), sulfameter (SME), trimethoprim (TMP) and sulfamerazine
196 (SMR) each had median concentrations that were higher than 11 ng L^{-1} (Fig. 1). The
197 median concentration of SMX in the lakes was 26.75 ng L^{-1} (Fig. 1), which is similar
198 to concentrations detected in several rivers, including the Yangtze River, China (from
199 <5 to 23 ng L^{-1}) (Chang et al. 2010) and the Seine River, France (from "not detected"
200 to 40 ng L^{-1}) (Tamtam et al.). The concentration of SMX in the lakes was also lower
201 than concentrations from the Nairobi River Basin in Kenya (from "below the limit of
202 quantification" to 13,800 ng L^{-1}) (Ngumba et al. 2016) and reservoirs in China (1.0 to
203 585 ng L^{-1}) (Peng et al. 2014). High SMX concentrations were observed in the bulk
204 water of Baiyangdian Lake, China (from "not detected" to 940 ng L^{-1}) (Li et al. 2012)
205 and Lake Lead, United States of America (0.28 to 1200 ng L^{-1}) (Park et al. 2014). The
206 median of the average SME concertation values was 16.95 ng L^{-1} (Fig. 1). which was
207 higher than concentrations from the Yellow Sea (from "not detected" to 1.2 ng L^{-1})
208 (Na et al. 2011) and the Daliao River, China (Jia et al. 2011). The highest SME
209 concentrations were observed in Honghu Lake, China, which had an average value of
210 54.9 ng L^{-1} (Wang et al. 2017c). The mean concentration of TMP in lake water
211 samples from across the Earth was 12.60 ng L^{-1} (Fig. 1). This concentration is
212 comparable to that seen in waters from the Jialing Jiang River, China (5 to 7 ng L^{-1})
213 (Chang et al. 2010) and much lower than those detected in the Pearl River, China
214 (56.4 to 605 ng L^{-1}) (Yang et al. 2011) and Haihe River, China (<LOQ-230 ng L^{-1})
215 (Luo et al. 2011). High TMP concentrations were found in Lake Ontario (from "not

detected" to 63.30 ng L^{-1}) in Canada (Li et al. 2010) and Lake Lead, United States of America (0.0015 to 120 ng L^{-1}) (Park et al. 2014).

Tetracyclines

Tetracycline (TC), oxytetracycline (OTC) and chlortetracycline (CTC) in lake water samples had median values of average concentrations exceeding 17 ng L^{-1} (Fig. 1). TC concentrations in the bulk water of most lakes were close to those of Bohai Bay (from "below the limit of quantification" to 30 ng L^{-1}) (Zou et al. 2011), lower than those in the Huangpujiang River (from "not detected" to 114 ng L^{-1}) (Jiang et al. 2011) and rivers in Hong Kong (30 to 497 ng L^{-1}) (Selvam et al. 2017). The OTC concentrations in most lakes were close to that of the Yangtze River (ND-22.5 ng L^{-1}) (Yan et al. 2013) and lower than Huangpujiang River (from "not detected" to 219.8 ng L^{-1}) (Chen and Zhou 2014) and rivers in Hong Kong (7-104 ng L^{-1}) (Selvam et al. 2017). High OTC concentrations (>50 ng L^{-1}) were found in Taihu Lake (Xu et al. 2014), Baiyangdian Lake (Cheng et al. 2014; Cheng et al. 2017) and Honghu Lake (Wang et al. 2017c). High CTC concentrations were found in the bulk water of Taihu Lake with different sampling times from May 2010 to December 2015 (Hu et al. 2017a; Xu et al. 2014; Zhou et al. 2016) and Honghu Lake (Wang et al. 2017c).

Quinolones

Fourteen types of quinolone antibiotics have been detected in lake waters (Table S3, Supplementary material I). Ofloxacin (OFL), norfloxacin (NOR) and ciprofloxacin (CIP) were the most frequent. NOR and OFL had median concentrations of more than 10 ng L^{-1} (Fig. 1), which were concentrations that are comparable to that of the

Jiulongjiang River (Zheng et al. 2011) and Yangtze River (Chang et al. 2010). High concentrations of NOR (57.04 ng L^{-1}) and OFL (376.39 ng L^{-1}) were also found in Baiyangdian Lake (Cheng et al. 2017).

Macrolides and lincosamides

Erythromycin (ETM), azithromycin, roxithromycin, lincomycin and clindamycin had median concentrations higher than 10 ng L^{-1}. The ETM concentrations in most studies were comparable to that of the Yangtze River, China (8 to 24 ng L^{-1}) (Chang et al. 2010) and lower than those of the Pearl River, China (40 to 560 ng L^{-1}) (Peng et al. 2011), Ume River, Sweden (80.3 to 160.5 ng L^{-1}) and Dal River, Sweden (347.4 to 694.8 ng L^{-1}) (Lindim et al. 2016). High ETM concentrations were observed in Baiyangdian Lake (Li et al. 2012) and Taihu Lake (Xu et al. 2014), both in China. High ROX concentrations were found in Baiyangdian Lake (from "not detected" to 155 ng L^{-1}) (Li et al. 2012) and Taihu Lake (from "not detected" to 218.3 ng L^{-1}) (Xu et al. 2014). The ROX concentrations in most lakes were comparable to that found in the Han River, South Korea (3 to 14 ng L^{-1}) (Choi et al. 2008b), as well as the Haihe River (from "not detected" to 12 ng L^{-1}) (Zou et al. 2011) and Songhuajiang River (0.2 to 11.5 ng L^{-1}) (Wang et al. 2017b) in China. High concentrations of lincomycin (357 ng L^{-1}) and clindamycin (503 ng L^{-1}) were detected in Taihu Lake, China (Wu et al. 2014).

Others

β-lactam (amoxicillin, oxacillin, ceftriaxone and cefazolin), quinoxaline (carbadox), polyether (narasin) and amphenicol (florfenicol, chloramphenicol and thiamphenicol)

antibiotics were seldom reported, in contrast to other groups of antibiotics (Table S5, Supplementary material I). However, the median values for florfenicol and chloramphenicol exceeded 10 ng L^{-1} (Fig. 1). The mean concentrations of chloramphenicol in Taihu Lake, China reached 32.5 ng L^{-1} (Zhou et al. 2016), which were similar to those observed in the Han River, Korea (31 ng L^{-1}) (Choi et al. 2008a).

3.2.2 Antibiotics in lake sediments

The average concentrations of thirty-five antibiotics in lake sediments from across the globe were collected and their median values and confidence intervals calculated (Fig. 2). Six of the antibiotics had median values that were less than 1 ng g^{-1}, including 3 sulfonamides and 3 quinolones. The median concentrations of the 21 antibiotics were in the range of 1 to 10 ng^{-1}. Only 8 antibiotics had median values that were higher than 10 ng g^{-1} (Fig. 2). These results indicate that the average concentrations of most antibiotics in lake sediments are often detected at concentrations less than 10 ng g^{-1}. SMX is a very well-studied sulfonamide antibiotic and has been recovered from the sediments from many lakes, including high concentrations in sediments from Honghu Lake, China (57.32 ng g^{-1}) and East Dongting Lake, China (30.57 ng g^{-1}) (Yang et al. 2016). TC had the highest median concentrations among the tetracycline antibiotics recovered from the sediment samples. High concentrations of TC were also found in lake sediments from Taihu Lake (Xu et al. 2014), Honghu Lake (Yang et al. 2016), and Baiyangdian Lake (Cheng et al. 2014), all in China. Baiyangdian Lake also had high ROX concentrations (from “not detected” to 302 ng g^{-1}) (Li et al. 2012).

3.2.3 Partition coefficient of antibiotics in lakes

A Mann-Whitney test shows that the median concentrations of the antibiotics and ARGs recovered from global lake water and lake sediment are significantly different ($p < 0.1$ level). Partitioning coefficients are important to understand the exchange of antibiotics between the water and sediment. The partitioning coefficients of antibiotics (Kd) between lake water and sediment have only been studied in two Chinese lakes, Bosten Lake (Lei et al. 2015) and Taihu Lake (Xu et al. 2014). Several Kd values were obtained or calculated from the data available from previous studies (Cheng et al. 2014; Zhang et al. 2015a; Zhang et al. 2018; Zhang et al. 2016; Zhou et al. 2016) (Table S6, Supplementary material I). A significant correlation was found between the log Kd values of the antibiotics and the log values of their octanol/water partition coefficients (Kow) in Bosten Lake ($p <0.1$); however, this correlation was not found for Taihu Lake (Fig. S2, Supplementary material I).

The normalized organic carbon distribution coefficients (Koc) of antibiotics were shown to be positively correlated with their Kow values in Chinese rivers (Li et al. 2018). However, Koc is not a suitable measure for antibiotics in Taihu Lake since antibiotics may bind to mineral surfaces more strongly than to organic matter (Xu et al. 2014). Strong sorption of tetracycline and oxytetracycline to sediments of Taihu Lake is due to cation exchange and complexation reactions between antibiotics and the charged and polar sites of sorbents (Ji et al. 2016). Different partition coefficients of multi-phase distributions of antibiotics discovered in Baiyangdian Lake further showed that colloid-bounding influenced the environmental behaviour of antibiotics in lakes (Cheng et al. 2017). Clearly, in contrast to the partitioning coefficient data in

304 rivers (Li et al. 2018), more research is needed to understand the behaviour and fate of
305 antibiotics in lakes.

306 **3.2.4 Spatial difference and temporal trend of antibiotics in lakes**

307 Due to the limited data available, only four antibiotics were used to compare lakes
308 from China and lakes from other countries worldwide. The results of the
309 Mann-Whitney test showed that there was no significant difference between SMX and
310 SMZ in lake water from China and lake water from other countries (Fig. 3). However,
311 the Chinese lakes showed significantly higher levels of NOR and OFL relative to
312 levels observed for the other countries ($p < 0.05$). High concentrations of antibiotics
313 frequently occurred in lakes in China (Fig. 3). These higher concentrations are
314 perhaps not entirely unexpected, because the country has the highest production and
315 usage of antibiotics (Zhang et al. 2015b).

316 Taihu Lake is one of the most heavily investigated lakes for antibiotic pollution (Ji et
317 al. 2016; Xie et al. 2015; Xie et al. 2017; Xu et al. 2014; Zhang et al. 2013; Zhong et
318 al. 2013; Zhou et al. 2016; Zhu et al. 2015). The mean concentrations of antibiotics
319 recovered from Taihu Lake have been recorded for over four years. Figure 4 shows a
320 possible temporal trend for antibiotic pollution. It is clear that the concentrations of
321 SMX and OFL in the water decreased from 2010 to 2015 ($p <0.05$ and $p <0.1$ levels,
322 respectively). The concentration of tetracyclines and SMZ, however, varied across
323 this time interval (Fig. S3, Supplementary material I). Within sediment samples, the
324 concentrations of SMX, sulfathiazole, SMZ, TC, OTC, CTC, OFL and NOR were
325 fairly similar between 2013 and 2014 (Zhou et al. 2016), and lower than those in 2010

326 (Xu et al. 2014) (Tables S1-S3, Supplementary material I). Although it is difficult to
327 determine a precise trend within the antibiotic pollution data available from Taihu
328 Lake, it does appear as though the pollution in the lake is lessening.

329 **3.2.5 Occurrence of antibiotics in aquatic biota**

330 Antibiotic pollution within aquatic biota from lakes is rarely reported and has only
331 been observed in Baiyangdian Lake (Li et al. 2012) and Taihu Lake (Xie et al. 2015;
332 Xie et al. 2017). Only 13 antibiotics have been detected in these aquatic biota, with
333 fewer antibiotics recovered from water than sediment samples (Table 2). Quinolones,
334 especially CIPs, play a particularly important role in the accumulation of antibiotics
335 among the aquatic plants of Baiyangdian Lake (8.37 to 6532 μg kg^{-1}) (Li et al. 2012).
336 Quinolones (17.8 to 167 μg kg^{-1}) and macrolides ("below the limit of detection" to
337 182 μg kg^{-1}), particularly ROX, NOR, and OFL, were frequently detected within
338 aquatic animals and birds (Li et al. 2012). The bioaccumulation factor (BAF) of
339 antibiotics in aquatic biota from Baiyangdian Lake reached upwards of 17 000 L kg^{-1}
340 (Li et al. 2012), while lower BAF values were found in Taihu Lake (Xie et al. 2015;
341 Xie et al. 2017). The BAF values for aquatic biotas from other lakes and several rivers
342 are summarized in Table 2 (Bai et al. 2014; Gao et al. 2012). BAFs were significantly
343 different for the various antibiotics. These differences could be due to lipid solubility
344 and the octanol-water partition coefficient (Kow) of antibiotics, as well as sampling
345 issues among the aquatic biotas (Li et al. 2012). pH is also an important factor
346 influencing BAFs and has previously been shown to influence the bioaccumulation of
347 antibiotics within *Daphnia* (Ding et al. 2016). "Bioaccumulative" chemicals are those

with BAFs greater than 5000 in aquatic organisms, and ‘‘potential bioaccumulative’’ chemicals are those with BAFs ranging from 2000 to 5000 (Gao et al. 2012). ROX, ENR and CIP are “bioaccumulative” chemicals, whereas SMZ, ETM, NOR and fleroxacin (FLE) are ‘‘potential bioaccumulative’’ chemicals. ENR and CIP showed higher BAFs than other reported antibiotics, and future studies should investigate their transport through the food chain.

3.3 Ecological risk of antibiotics

The inhibitory effects of antibiotics on aquatic biota depend on the type and dose of antibiotic, as well as the organisms sampled (Liu et al. 2014; Magdaleno et al. 2015). The HC_5 values of 17 antibiotics on aquatic biota ranged over 3 orders of magnitude (Fig. 5a and Table S7, Supplementary material I). The HC_5 of ETM was 11.73 μg L^{-1}, the lowest value among the antibiotics analysed. The vast majority of antibiotics had HC_5 values less than 100 μg L^{-1}, and only TMP was higher than 1500 μg L^{-1}. To better elucidate the ecological risk of antibiotics in lake water, the HQ values of mean concentrations of antibiotics in the lakes were analysed. HQ values ≤ 0.1 indicated an insignificant ecological risk, whereas HQ values < 0.1 and ≤ 1 represented a low ecological risk, values from 1 < and ≤ 10 were a moderate ecological risk, and HQ > 10 represented a high ecological risk (Ågerstrand and Rudén 2010). Notably, all the HQ values of the antibiotics examined here were below 0.1 (Fig. 5b); hence, there does not appear to be any significant ecological risk to aquatic biotas from antibiotics. ETM had the highest median HQ values, followed by clarithromycin (CLA) (Fig. 5b). ETM has previously been identified as a potential ecological risk to aquatic biotas in

370 rivers of China (Bu et al. 2013; Chen et al. 2017). Additionally, ETM, CLA, and
371 azithromycin were included on a watch list of substances that could pose a significant
372 ecological risk for aquatic environments in countries within the European Union
373 (Välitalo et al. 2017). These results indicate that the macrolides in lakes worldwide
374 may need special attention due to the ecological risk they pose. These values could
375 also be used as references to evaluate the ecological risk of antibiotics in freshwater
376 systems.

377 **4. Antibiotic resistance genes in lakes**

378 **4.1 ARGs in lakes using culture-dependent methods**

379 Antibiotic resistant bacteria (ARB) have been regarded as a threat to human health
380 since the 1970s (Grabow et al. 1974). They have been isolated from lakes since the
381 1980s (Jones et al. 1986). *Escherichia coli*, *Enterococcus* and *Pseudomonas* are
382 among the most frequency isolated, but, more recently, ARGs within ARBs have been
383 discovered. ARGs found most frequently in *E. coli* from Hamilton Harbour, Lake
384 Ontario, Canada were *tetA*, *tetB*, bla_{TEM}, *aadA1* and *sulII* (Hamelin et al. 2006). In
385 organic-rich bacteria-contaminated sediments of Lake Geneva, Switzerland, 22% -
386 48% of *E. coli* and 16% - 37% of *Enterococcus* (ENT) carried bla_{TEM} (Thevenon et al.
387 2012). The most abundant resistance profile was seen in the resistance clones of 29
388 ARGs from Jinshan Lake, China; collectively, 88% of TC-resistant, 94% of
389 SMX/TMP-resistant, 90% of ampicillin-resistant, 78% of streptomycin-resistant, and
390 72% of quinolone-resistant clones can be described by their corresponding ARGs
391 (Wang et al. 2013). Among the extended spectrum beta-lactamase genes in bacteria

392 from Taihu Lake, China, bla_{TEM} was the most abundant, followed by bla_{SHV}, and
393 bla_{CTM-X} was the least abundant (Yin et al. 2013). Most of the bacteria isolated from
394 urban lakes in China carried at least two different functional ARGs; among these
395 bacteria, gram-negative isolates had a higher detection frequency of ARGs than
396 gram-positive isolates (Zhang et al. 2016).

397 **4.2 ARGs in lakes based on qPCR and metagenomic methods**

398 A total of 17 studies used culture-independent methods to quantify the abundance of
399 ARGs in lakes (Tables S1-S2, Supplementary material II). The lakes assessed in the
400 17 included studies are located in the United States of America, Switzerland, Italy,
401 India, Sweden, and China. Notably, nearly 50 published reports studied ARG
402 abundance in rivers (Tables S1-S3, Supplementary material II). Additionally, 45
403 identified studies assessed the abundance of antibiotics in lakes.

404 Among the studies that assessed rivers, 34, 10, and 3 used qPCR, metagenomics, and
405 high-throughput PCR (HT-PCR), respectively. Among the studies that assessed lakes,
406 14 used qPCR and 3 used metagenomics. HT-PCR has been used for ARG analysis of
407 samples from swine farms (Zhu et al. 2013), rivers (Ouyang et al. 2015; Zheng et al.
408 2017; Zhou et al. 2017), and drinking water treatment plants (Xu et al. 2016).
409 Although different issues arose in the studies that employed HT-PCR, this method still
410 appears to be very promising, particularly because it is capable of processing a large
411 number of samples simultaneously and detecting a large number of ARGs per sample
412 (Lamas et al. 2016). HT-PCR may be an important alternative tool to conventional
413 qPCR for ARG analysis in lakes.

414 A metagenomic analysis showed that Kazipally Lake, India was contaminated by
415 fluoroquinolones and had a higher level of ARG abundance than the non-polluted
416 Nydalasjön Lake, Sweden (Bengtsson-Palme et al. 2014). The abundances of ARGs in
417 sediments of Lake Michigan, USA (Chu et al. 2017) and pristine Lake Namco and
418 Qiangyangyong Glacier Lake, China (Chen et al. 2016) were also lower in
419 comparison with effluents from sewage treatment plants. The *sul2* and *qnrD* genes
420 were the most common ARGs in Kazipally Lake (Bengtsson-Palme et al. 2014), while
421 the *bacA* gene was the most prevalent and dominant in pristine lakes on the Tibetan
422 Plateau (Chen et al. 2016).
423 Sulfonamide resistance genes (*sul*) and tetracycline resistance genes (*tet*) were the
424 most studied ARGs in lakes and rivers (Tables S1-S3, Supplementary material II). In
425 lake water, the abundance of *sul1* is usually higher than that of *sul2* ($p < 0.1$ level).
426 However, there is no significant difference between the relative abundances of *sul1*
427 and *sul2* from lake and river water (Fig. 6). For the *sul1* gene, abundances in urban
428 lakes in China (Yang et al. 2017b), 21 Swiss lakes (Czekalski et al. 2015), and Lake
429 Geneva (Czekalski et al. 2012) were detected at 10^{-3} to 10^{-2} copies per 16S rRNA
430 level. These levels are higher than those from Bosten Lake (10^{-5} to 10^{-3} copies per 16S
431 rRNA) (Zhou et al. 2014) and similar to those from the Liuxi River (Xiong et al.
432 2014). The abundance of the *tetA* gene reached upwards of 10^6 copies per mL in Lake
433 Maggiore (Di Cesare et al. 2015) and 10^5 copies per mL in Taihu Lake (Zhang et al.
434 2009c). These abundance levels were higher than those in the Huangpujiang River
435 (10^3 copies per mL) (Jiang et al. 2013) and Lake Superior (LaPara et al. 2011).

All absolute abundances of *sul1* in lake sediments were in the range 10^{-6} to 10^{-10} copies per gram of sediment, which showed no difference compared with those in rivers (p = 0.84) (Fig. 6). Lake Geneva had a comparatively high abundance of *sul1*, with a value of 2.2×10^{9} copies per gram of sediment (Czekalski et al. 2014). The abundance of *tet* genes in sediments of Taihu Lake (Zhang et al. 2009c) and Lake Geneva (Czekalski et al. 2014) reached upwards of 10^{6} copies per gram, which is comparable to those in the Almendares River (Knapp et al. 2012). The abundance of *sul* genes was higher than that of *tet* genes in Lake Geneva (Czekalski et al. 2014) and 15 lakes along the Yangtze River (Yang et al. 2017a). Similar results were found in the sediments of the Haihe River (Dang et al. 2017) and Xiangjiang River (Xu et al. 2017). For other types of ARGs, the abundances of ARGs in Taihu Lake were found in the following order: *strB* > *qnrB* > s*trA* > *qnrS* (Han et al. 2013). The relative abundances of bla_{TEM}, *aadA*, bla_{CTX-M}, and bla_{SHV} were higher than that of bla_{NDM} in Lake Geneva sediments (Devarajan et al. 2015).

4.3 The role of microbial community and mobile genetic elements in ARG propagation

Microbial community adaptation to pollutants or wastewater can result in changes in the ARG profile through several independent mechanisms, including (i) selective enrichment of a population (clonal amplification of ARB), (ii) advantageous mutations or gene rearrangements and duplication, and (iii) horizontal transfer of ecologically important genes, such as ARGs (Kondrashov 2012; Oh et al. 2013). Increases in ARG abundances are related to an increased number of possible ARBs in

458 the environment; this phenomenon was observed for the ARG abundance and number
459 of *Enterobacteriaceae* in lakes in Brazilian zoos (de Faria et al. 2016) and
460 *Bacteroidales* in rivers (Jia et al. 2014). Increased levels of ARGs and significant
461 changes in the microbial community were adapted to the wastewater effluent in Lake
462 Michigan (Chu et al. 2017) and antibiotic pollution in Kazipally Lake
463 (Bengtsson-Palme et al. 2014). The bacterial community was identified as a
464 contributing factor driving ARG composition other than mobile genetic elements
465 (MGEs) in Tiaoxi River (Zheng et al. 2017) and Wen-Rui Tang River (Zhou et al.
466 2017).
467 The horizontal gene transfer (HGT) frequency of ARGs in aquatic bacteria was higher
468 than that in terrestrial bacteria (Hu et al. 2016). Transformation, transduction, and
469 conjugative transfer are the main mechanisms of HGT (Thomas and Nielsen 2005).
470 Mobile genetic elements, such as plasmids, transposons, insertion sequences and
471 integrons, are the important carriers in HGT of ARGs (Stokes and Gillings 2011). In
472 Lake Michigan, high proportions of plasmid-associated ARGs were found in
473 sediments, ranging from 32% to 100% of the total identified ARGs (Chu et al. 2017).
474 Even in the pristine sediments from Lake Namco and Qiangyong Glacier Lake, a
475 variety of integrons and plasmids existed, among which pGMI1000MP plasmid and
476 CH34 megaplasmid were some of the most abundant (Chen et al. 2016). In an
477 antibiotic-polluted Indian lake, 26 known and 21 putative novel plasmids were
478 recovered in the lake metagenome (Bengtsson-Palme et al. 2014). A drastic increase
479 in the abundance of integron integrases and ISCR elements was also found in the Ter

River, Spain after the river received some treated wastewater discharge (Lekunberri et al. 2018).

The class 1 integron (*intI1*) is one of the main vectors for HGT of ARGs in the environment. Nearly 40% of the isolated bacteria in Taihu Lake had *intI1* (Yin et al. 2013), which may facilitate the spread of ARGs between different bacteria. *intI1* has a significantly positive relationship with the abundance of ARGs in the aquatic environment, such as sediment samples from 15 lakes along the Yangtze River (Yang et al. 2017a), water from urban lakes (Yang et al. 2017b), the Haihe River (Dang et al. 2017) and the Tiaoxi River (Zheng et al. 2017). Interestingly, the relative abundances of *intI1* in lakes and rivers showed no significant difference in comparison with those in wastewater treatment plant sludges and treatment plant effluent via meta-analysis (Gillings 2018). The lack of a difference seems to further confirm that integrons play an important role in the HGT of ARGs in environment. Identification of the transfer of the mobile resistome in bacteria by bioinformatic analysis suggests that the transfer is mainly controlled by bacterial community composition (Hu et al. 2017b; Hu et al. 2016). Therefore, ARG propagation under selection pressure in lakes may mainly occur through enrichment of specific populations (ARB) and HGT of ARGs between different bacterial taxa.

4.4 Factors influencing ARG distribution in lakes

Chemical pollution

Chemical pollution discharged into lakes, such as antibiotics and heavy metals, may exert selection pressure on ARGs. The effects of antibiotics on ARG distribution

502 varied in each study. The positive pressure of antibiotics on ARG distribution in field
503 surveys has been observed and/or analysed in East Dongting Lake, Honghu Lake
504 (Yang et al. 2016), and Kazipally Lake (Bengtsson-Palme et al. 2014). Similar results
505 were also observed in rivers in Pakistan (Khan et al. 2013) and China, including the
506 Haihe River (Luo et al. 2010), Pearl River (Chen et al. 2015) and Beijiang River (Zou
507 et al. 2009). However, a significant pressure of antibiotics on ARG distribution was
508 not seen in rivers in South Africa (Suzuki et al. 2015) and Vietnam (Nakayama et al.
509 2017). OTC levels were even negatively correlated with the abundance of the *tetL*
510 gene in Drweca River, Poland (Harnisz et al. 2015). In experimental settings, no
511 observable effect of antibiotics on ARG abundances was found in lake sediment
512 microcosms (Berglund et al. 2014). Increased selection on tetracycline resistance
513 genes was apparent at exposure levels as low as 20 μg L^{-1} OTC in some aquatic
514 systems (Knapp et al. 2008). A recent study also showed that *in situ* degradation of
515 antibiotics prevails at high concentrations of sulfonamides (5000 ng L^{-1}), whereas
516 physiological adaptation by ARG spread would be more important under relatively
517 lower concentrations of sulfonamides (1000 ng L^{-1}) (Vila-Costa et al. 2017).
518 Therefore, studies that assess the selection pressure induced by the presence of
519 antibiotics on the persistence and evolution of resistance genes in lakes, especially the
520 long-term impact on antibiotics at environmental concentrations, are clearly required
521 to help understand this relationship.
522 Heavy metals are another important factor influencing ARG distribution. The level of
523 heavy metal contamination is several orders of magnitude greater than antibiotic

pollution (Stepanauskas et al. 2006) and may exert co-selection on ARGs (Baker-Austin et al. 2006; Di Cesare et al. 2016; Seiler and Berendonk 2012). Heavy metals have been regarded as a main cause of ARG contamination in sediments of Lake Geneva, Switzerland (Czekalski et al. 2014; Devarajan et al. 2015). Similar results were also found for the effect of heavy metals at sub-lethal levels on ARG distribution in the Xiangjiang River, China (Xu et al. 2017). Antibiotics and co-selection with heavy metals further accounted for the variation of ARGs in the bulk water of urban lakes (Yang et al. 2017b). In contrast, no relationship between ARGs and heavy metals was found in sediments from Chaohu Lake, China (Wu et al. 2016).

In addition, other pollutants have also been found to enrich ARGs in certain environments, including biocides and chemical preservatives (Romero et al. 2017). Biocide (benzyldimethyldodecyl ammonium chloride) at environmental concentrations (10 μg L^{-1}) enriches specific ARGs, such as $bla_{CTX\text{-}M}$ and *tetA*, in natural water from eutrophic lakes (Yang and Wang 2018). Even persistent organic pollutants, such as polycyclic aromatic hydrocarbons, unexpectedly accelerated the propagation of ARGs in coastal water (Wang et al. 2017a). Nanoparticles also helped shape the microbial community and increased the abundance of ARGs (Metch et al. 2018). Based on these findings, more comprehensive studies are needed to understand the individual and co-selection role of chemical pollution at environmental levels on the propagation of ARGs in lakes.

Physicochemical factors

546 The organic matter in the sediment was an important factor influencing ARG
547 distribution in Lake Geneva (Devarajan et al. 2015) and Chaohu Lake (Wu et al.
548 2016). In Lake Maggiore, on the Italian-Swiss border, the abundance of *tetA* and *sul2*
549 in bulk water was positively correlated with dissolved oxygen and negatively
550 correlated with chlorophyll *a* (Di Cesare et al. 2015). Total organic carbon and total
551 dissolved nitrogen were also positively correlated with the absolute abundance of total
552 ARGs in urban rivers (Zhou et al. 2017). Conductivity, salinity, and dissolved oxygen
553 concentration in Warta River, Poland were positively correlated with the abundance of
554 sulfonamide resistance genes (Koczura et al. 2016). Unlike most living organisms,
555 dissolved oxygen in lakes is not necessary for some bacteria to survive and shape the
556 bacterial community (Baatar et al. 2016). As suggested by Di Cesare et al. (2015),
557 resistant microbes inhabit specific niches in lakes or the aquatic environment.

558 *Human activities*

559 Human activities result in the input of ARGs into lakes through several ways,
560 including effluent from hospitals and wastewater treatment plants (Guo et al. 2017;
561 Rizzo et al. 2013; Zhang et al. 2009b) and runoff or discharge from agriculture,
562 aquaculture, and animal husbandry (Heuer et al. 2011; Seiler and Berendonk 2012;
563 Zhu et al. 2013) (Fig. 7). The parameters for evaluating the effect of human activities
564 on ARGs in lakes are usually the number or capacity of wastewater treatment plants
565 (WWTPs), distance to the point source (e.g., WWTP, hospital, aquaculture sites), and
566 landscape (e.g., urban area, agriculture area), which can also be an indicator for
567 pollution levels. Swiss lakes with a greater number and capacity of WWTPs in the

568 catchment usually exhibited high abundance of *sul1* (Czekalski et al. 2015). Similar
569 results were also observed in the South Platte River Basin, USA where *sul1*
570 abundances in river sediments were correlated with upstream capacities of animal
571 feeding operations and wastewater treatment plants (Pruden et al. 2012). A high
572 relative abundance of ARGs was also found in sites close to the sewage discharge
573 point in Lake Geneva (Czekalski et al. 2014). A high abundance of *sul* and *tet* genes
574 was additionally found in lakes along the Yangtze River, particularly near lakes with a
575 high proportion of built-up land (Yang et al. 2017a). Similarly, Nanhu Lake and Shahu
576 Lake, which are located in a high-density building area of China with elevated human
577 activities, had a high relative abundance of total ARGs (Yang et al. 2017b).

578 **4.5 The role of aquatic biota in the spread of ARGs.**

579 Aquatic biotas play an important role in the propagation of ARGs but few studies
580 have focused on this topic. *Daphnia* has been shown to be a refuge for ARGs in
581 freshwater communities, where bacterial taxa associated with *Daphnia* were potential
582 carriers of *tetA* (Eckert et al. 2016). Bacteriophages in sewage and rivers have also
583 been uncovered as reservoirs for ARGs and could accelerate the spread of ARGs
584 (Colombo et al. 2017; Colomer-Lluch et al. 2014; Colomer-Lluch et al. 2011). In the
585 non-aquaculture freshwater Lake Mogan, Turkey, antibiotic resistance is common
586 among the phenotypes of the fish-mucus-dwelling bacterial populations (Ozaktas et al.
587 2012). In fish farms, fish faeces contributed to ARG enrichment in sediments despite
588 a lack of contemporaneous antibiotic treatments at the farms and different resistome
589 compositions in the intestinal contents of individual farmed fish (Muziasari et al.

2017). The hindgut of zebra fish was the most important intestinal region supporting ARG dissemination and helped promote the spread of ARG into the water environment (Fu et al. 2017). Shrimp in Iskenderun Bay, Turkey also harbour multi-resistant bacteria that may propagate dissemination of ARGs in the environment (Matyar et al. 2008). Different aquatic plant species and tissues contained vastly different bacterial communities (Crump and Koch 2008), which may affect the composition and transport behaviours of ARGs. Clearly, aquatic biotas are an important carrier and/or refuge for ARGs and a useful media for the exchange of ARGs between aquatic biota and the environment (Fig. 7). A broad range of niches, not only bacteria but also phages, aquatic plants and animals, therefore, should be considered when the enrichment, fate and transport of ARGs in lakes are evaluated.

4.6 **Potential risk of ARGs in lakes to humans**

Unlike antibiotics, there is no available method to calculate the potential risks to humans based on the presence of ARGs in lakes. Risk assessment frameworks of antibiotic resistance have been proposed and include hazard identification, hazard assessment/characteristics, exposure assessment, and risk assessment (Chereau et al. 2017; Manaia 2017). However, there are many factors hindering the risk assessment of ARGs in lakes for human health, such as the uncertain affiliation between bacterial taxa and ARGs (Manaia 2017), and the unclear doses of ARB for various health outcomes and pathways (Ashbolt et al. 2013). The exposure pathways of ARGs in lakes to humans can be classified into three categories: (1) ingestion of water containing ARGs, (2) ingestion of aquatic products, and (3) direct contact with the

612 lake, such as recreation and swimming (Chereau et al. 2017; Eckert et al. 2018) (Fig.
613 7). Regarding the exposure frequency, the ingestion of lake water containing ARGs
614 (i.e., drinking water) is the main risk to humans. Many lakes are important drinking
615 water sources for humans, including Lake Michigan, Lake Geneva, and Lake Zurich.
616 Recent studies have shown that bacteria and ARGs were still present in tap water after
617 treatment, though significantly reduced (Su et al. 2018). In one case, the relative
618 abundance of ARGs in drinking water even increased after chlorination (Jia et al.
619 2015). Chlorine disinfection is not able to destroy antibiotic-resistance genes, but it
620 can inactivate and decrease bacterial counts of ARBs (Furukawa et al. 2017). ARGs in
621 inactive bacteria or naked DNA persist and may propagate through HGT to elevate
622 the risk to humans. Therefore, regarding the risk of ARGs to humans, both ARGs in
623 active bacteria and naked DNA must be considered. Comprehensive analyses of the
624 persistence of ARGs in environment and their resistance to conventional drinking
625 water treatment methods are also important to develop a priority list of harmful ARGs
626 to humans.

627 **5. Perspectives of study on antibiotics and ARGs in lakes**

628 **5.1 Priority lists of harmful antibiotics in lakes**

629 Fifty-seven kinds of antibiotics were detected in lakes worldwide; however, many
630 antibiotics, such as oxazolidinones and ansamycins, have not yet been investigated in
631 lake environments and were not included here. Additionally, metabolites of antibiotics,
632 again not studied here, may be harmful to the aquatic environment and have not yet
633 received sufficient study (Baumann et al. 2015). The non-targeted, large screening of

634 over a thousand emerging contaminants is possible through ultra-high-performance
635 liquid chromatography coupled with quadrupole time-of-flight mass spectrometry
636 (UHPLC-QTOF MS) (Hernández et al. 2015). This technique could be a powerful
637 tool for the analysis of antibiotics and their metabolites in lakes. This information
638 could be combined with BAFs and ecotoxicology data to develop a priority list of
639 harmful antibiotics in the aquatic environment and assist in lake management.

640 **5.2 The relationship between chemical pollution and ARGs**

641 Some of the antibiotics detected in the lakes studied here were sulfonamides,
642 tetracylclines, quinolones and macrolides. The most common types of ARGs detected
643 in lakes were *sul* and *tet* genes. Additional types of ARGs were discovered using the
644 metagenomic method and HT-qPCR, such as ARGs based on the antibiotics to which
645 they conferred resistance: aminoglycosides, β-lactams, chloramphenicol,
646 macrolide-lincosamide-streptogramin B (MLSB), and vancomycin (Zheng et al. 2017;
647 Zhu et al. 2017). However, few studies have conducted a combined analysis of
648 antibiotics and ARGs. The large-scale screening of organic pollutants, including
649 antibiotics and heavy metals, and ARG profiles should be applied to develop a more
650 comprehensive understanding of the relationship between chemical pollution and
651 ARGs in freshwater lakes. In addition, a good understanding of the lake microcosm or
652 macrocosm is needed to evaluate the individual and co-selection role of chemical
653 pollution on the propagation of ARGs in lakes at their environmental level. This
654 approach is useful to identify the main pollutants exerting selection pressure on ARG
655 propagation and influencing the persistence of ARGs in lakes.

5.3 ARGs and bacterial communities in lakes

The antibiotic resistance of *Escherichia coli*, *Enterococcus* and *Pseudomonas* present in lakes has been well studied and provides important information about the transfer of ARGs in the bacterial community. Furthermore, there is still a significant difference between the profile of ARB via metagenomic analysis and culture-dependent ARB communities (Narciso-da-Rocha and Manaia 2016). Moreover, ARGs and their affiliated taxa are still very unclear. Hence, culture-independent methods should be used with culture-based approaches to identify major sources of ARB profiles. This would help to understand the composition of ARB in the bacterial community in freshwater lakes and assess the transfer risk between lake ARB and humans. It would also be beneficial to study the evolution of ARGs in different bacterial taxonomic groups based on isolated bacteria and their ARG sequences.

5.4 Transport of antibiotics and ARGs in lakes

Specific hydraulic conditions in lakes, such as long retention of water exchange, may result in special characteristics in the antibiotic distribution and ARG spread in the lake ecosystem. Furthermore, lake sediments can be used as natural archives of perturbation histories, including acidification, eutrophication, and pollution; lake sediments can also provide important information on the historical trend of chemical pollution and ARGs (Anderson 1995; Eckert et al. 2018). Lakes are clearly an important environment to investigate the fate of antibiotics and spread of ARGs (Fig. 7). Once chemical pollutants (e.g., antibiotics and heavy metals) are discharged into lakes via runoff or rivers, partitioning between water and sediment can occur, and, via

disturbance, sediment could be a secondary pollution source. Antibiotics can also accumulate in aquatic biota through the food chain. ARGs discharged into the environment will be enriched, selected, or transferred between different bacterial taxa under the selection pressure of chemical pollution. ARG carriers, such as bacteria, phages, and even extracellular DNA, can be adsorbed on the surface of aquatic biota or inhaled into the alimentary canal of aquatic animals. The faeces from these aquatic animals or their decomposing bodies release ARGs into the sediment, resulting in changes in the ARG composition of sediments. Antibiotics and ARGs in water, sediment, and aquatic biota should be studied to give a more complete understanding of their relationship and to better assess the fate and risk of antibiotics, ARGs and ARB in freshwater lakes.

6. Conclusion

This paper systematically reviewed the distribution of antibiotics and ARGs in global lakes. A total of 57 antibiotics reported at least once in the water and sediments of global lakes were assessed. The concentrations of these antibiotics in lake water were higher than those in lake sediment. As seen from our meta-analysis, sulfamethoxazole, sulfamerazine, sulfameter, tetracycline, oxytetracycline, erythromycin, and roxithromycin were found at high concentrations in both the lake water and sediment. There was also no significant difference in sulfamethoxazole and sulfamethazine concentrations in lake waters from China and the lake water from other countries worldwide; however, there was a significant difference in ofloxacin and norfloxacin concentrations between lake waters from China and from the rest of the world. The

concentration of sulfamethoxazole and ofloxacin in bulk water from Taihu Lake significantly decreased between 2010 and 2015. ROX, ENR and CIP are "bioaccumulative" chemicals in aquatic organisms, whereas ETM had the highest ecological risk based on hazard quotient. There was also no significant difference in the concentration of *sul* genes in rivers and lakes. Chemical pollution, including antibiotics and heavy metals, influenced the distribution of ARGs in lakes through selection pressure. The bacterial community is the principle force in shaping the resistome, followed by mobile genetic elements.

Unfortunately, the continuous discharge of chemical pollutants into lakes will not be readily solved in the near future, and selection pressure on ARGs in lakes will continue. It is therefore urgent that we (1) develop priority lists of antibiotics and their metabolites in lakes; (2) identify some of the key pollutants influencing ARG propagation for proper lake management; (3) identify the persistence of ARGs in the environment and their resistance to conventional drinking water treatment methods; (4) understand the long-term ARG propagation exerted by individual or combined pollutants at environmental concentrations; and (5) understand the role of aquatic biota in the transport of antibiotics and ARG propagation.

Declaration of interest

None

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Table 1 The number of studies and detected number of each class of antibiotics in global lakes

Class	China		Other Countries	
Water	N[a]	n[b]	N	n
Sulphonamides and Trimethoprim	22	16	20	14
Tetracyclines	14	4	1	3
Quinolones	18	12	10	10
Macrolides and Lincosamides	9	10	8	7
Others	3	4	3	3
Sediment	N	n	N	n
Sulphonamides and Trimethoprim	10	15	0	0
Tetracyclines	7	4	0	0
Quinolones	9	11	1	4
Macrolides and Lincosamides	7	9	1	5
Others	3	5	1	1

[a]: number of studies, [b]: number of studied compounds

1295 Table 2 Comparison of bioaccumulation factors of antibiotics in freshwater system (Unit: L kg^{-1}).

Aquatic biota	SMZ	SMX	SDM	SCM	TC	OTC	ROX	ETM	OFL	NOR	ENR	FLE	CIP
Aquatic plants and algae													
Aquatic plants										554-4400 [a]	653-2590 [a]		10200-170000[a]
Algae		25-183 [b]			30-977 [b]		28-2352[b]; 100-254[c]	NA [b]; 8.7-162[c]	60-375 [b]	27-639[b]			38-1202 [b]
Invertebrates													
Daphnia magna							13.4-93.5[d]						
Snail							667[c]	4.4[c]			6140 [a]		
Mussel, snail and bivalve		39-94 [b]			42-577 [b]		811-6352 [b]	447-3511 [b]	11-327 [b]	42-2780 [b]			99-4067 [b]
Mussel							406[c]						
Crab		27-65[e]				157[e]	195[e]			9[e]	11050-34508[e]		
Bivalve							510[c]	32[c]					
Shrimp		7.7-131 [b]			4.6-159 [b]		43-1704[b]; 294[c]	NA [b]		84-3125[b]	16600[a]	4050 [a]	45-933 [b]

Fish												
Carp	1672[f]					7410[a]; 200-376[c]	32[c]; 4492[f]		284[f]	4490 [a]		3262[f]
Blunt snout bream											4130[a]	
Topmouth gudgeon	3870 [a]											
Fish		NA [b]; 13[e]	339[e]		3.1-362 [b]	17-3668[b]; 139[c]	35-2029 [b]; 44[c]; 52[e]	12-970 [b]	35-2038[b]	12059[e]		23-13552 [b]
Lake anchovy						665[c]	3.8[c]					
Xingkai bitterling			527[e]	232[e]		5290[e]	164[e]			45407[e]		
Crucian		13[e]	355[e]							31241[e]		

[a](Li et al. 2012); [b](Xie et al. 2017) ;[c](Xie et al. 2015) ; [d](Ding et al. 2016); [e](Bai et al. 2014); [f](Gao et al. 2012)

Sulfamethazine: SMZ; Sulfamethoxazole: SMX; Sulfadimethoxine: SDM; Sulfacetamide: SCM; Tetracycline: TC; Oxytetracycline: OTC; Roxithromycin: ROX; Erythromycin: ETM; Ofloxacin: OFL; Norfloxacin: NOR; Ciprofloxacin: CIP; Enrofloxacin: ENR; Fleroxacin: FLE.

Figure Captions

Fig. 1 The median values and 95% confidence intervals of average concentrations of antibiotics in bulk water of global lakes (ng L^{-1}, the number in the parentheses indicate the counts of data; invalid confidence intervals were not shown in the figure).

Fig. 2 The median values of average concentrations of antibiotics in sediment of global lakes (ng g^{-1} dry weight, the number in the parentheses indicate the counts of data; invalid confidence intervals were not shown in the figure).

Fig. 3 The comparison of antibiotics in bulk water in lakes between China and other countries worldwide (n, the data number). Different letters over the bars indicate statistically significant differences at $p < 0.05$ level.

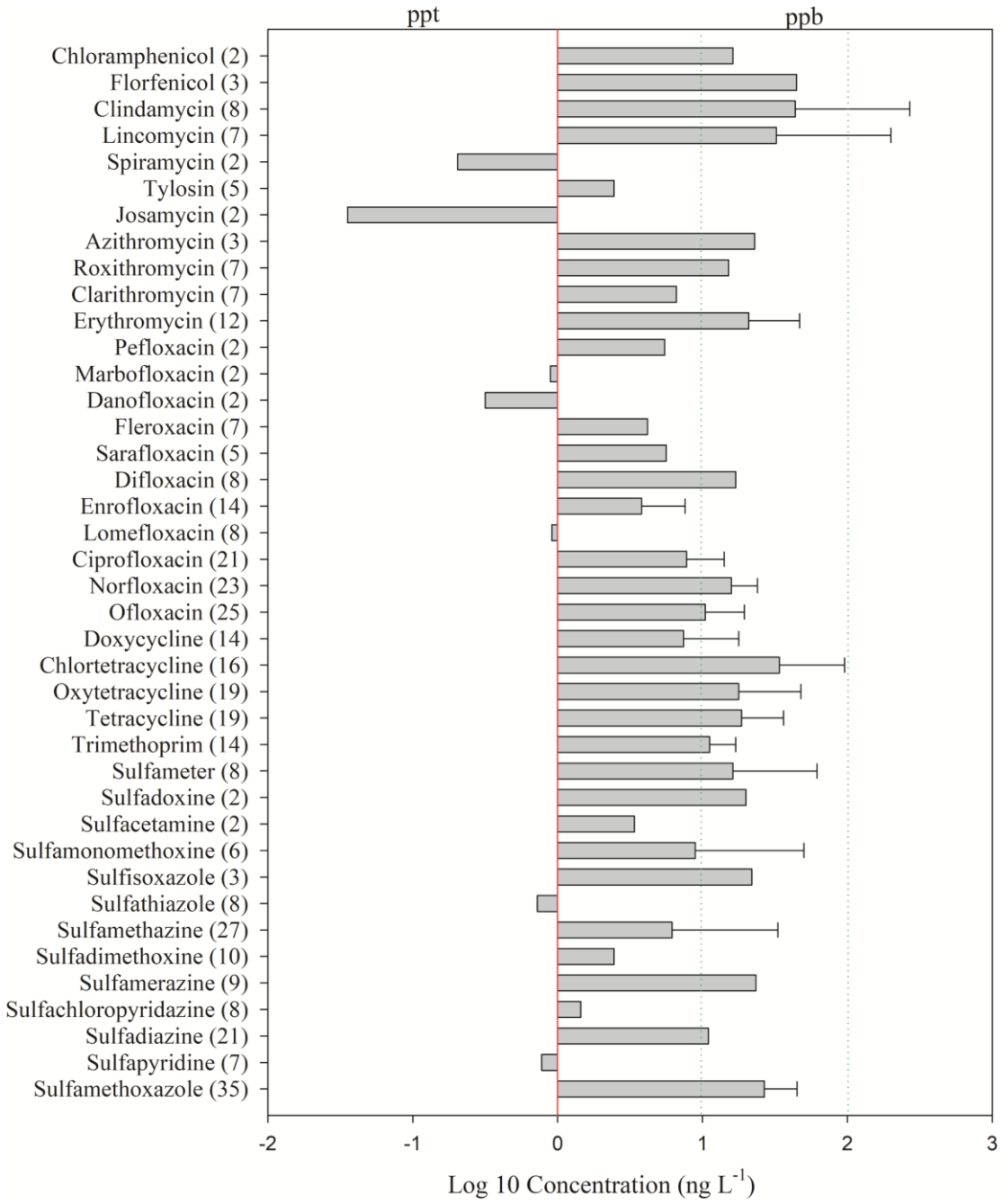
Fig. 4 The temporal trend of antibiotics in bulk water from Taihu Lake (a: (Xu et al. 2014); b: (Yan et al. 2014); c: (Wu et al. 2014) ; d: (Zhou et al. 2016); e: (Hu et al. 2017a), The number was the counts of sampling sites; sulfamethoxazole concentrations in 2013 was the mean values of the two references).

Fig. 5 The hazardous concentration for five percent of the species (HC_5) and their 2.5th and 97.5th percentile values for antibiotics on aquatic system (a) (Unit: μg L^{-1}; the number in the parentheses indicate the counts of species) and hazard quotient of antibiotics in freshwater lakes (b) (Sulfamethoxazole: SMX; Sulfadiazine: SDZ; Sulfamethazine: SMZ; Trimethoprim: TMP; Tetracycline: TC; Oxytetracycline: OTC; Chlortetracycline: CTC; Ofloxacin: OFL; Norfloxacin: NOR; Ciprofloxacin: CIP; Lomefloxacin: LOM; Enrofloxacin: ENR; Erythromycin: ERY; Clarithromycin: CLA; Lincomycin: LIN).

Fig. 6 The comparison of *sul* genes in bulk water and sediment between lakes and rivers (n, the number of studies).

Fig. 7 The transport of antibiotics and ARGs in different media and their possible exposure ways to human health (A: chemical pollutants and ARGs from sewage treatment plants and hospitals; B: chemical pollutants and ARGs from agriculture, aquaculture and animal husbandry; C: drinking water, D: recreation and swimming; E: ingestion of aquatic food; ① the sedimentation of pollutants from water; ② the

resuspension of pollutants from sediment; ③ the microbial community and resistome changed due to the selection pressure of chemical pollution; ④ chemical pollutants accumulated by aquatic biota; ⑤ chemical pollutants and ARGs released from feces or dead body of aquatic animals; ⑥ ARGs ingested or adsorbed by aquatic biota; ⑦the transport of chemical pollutants and ARGs between aquatic biota).



1335

1336 **Fig. 1**

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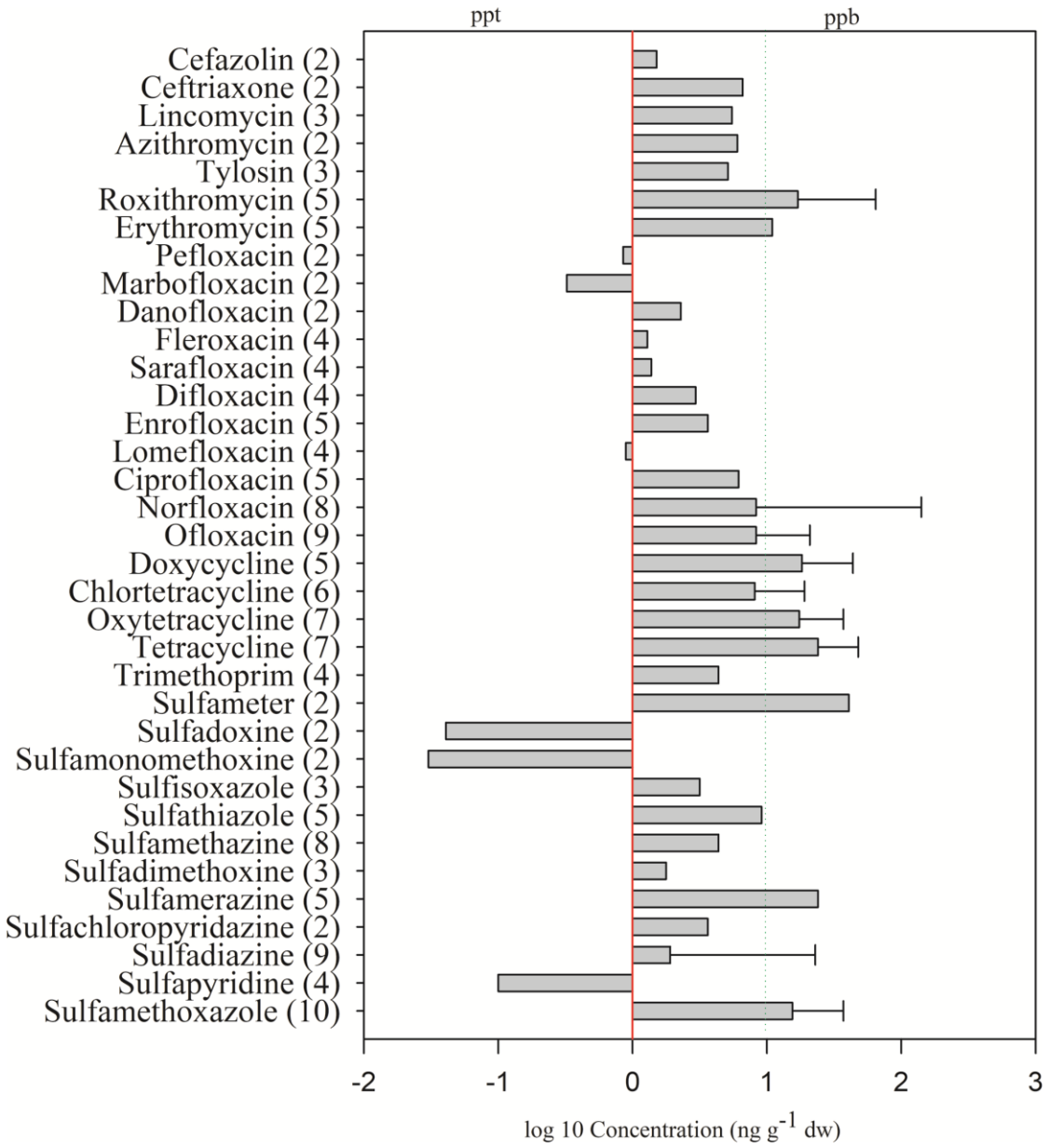


1338

1339 **Fig. 2**

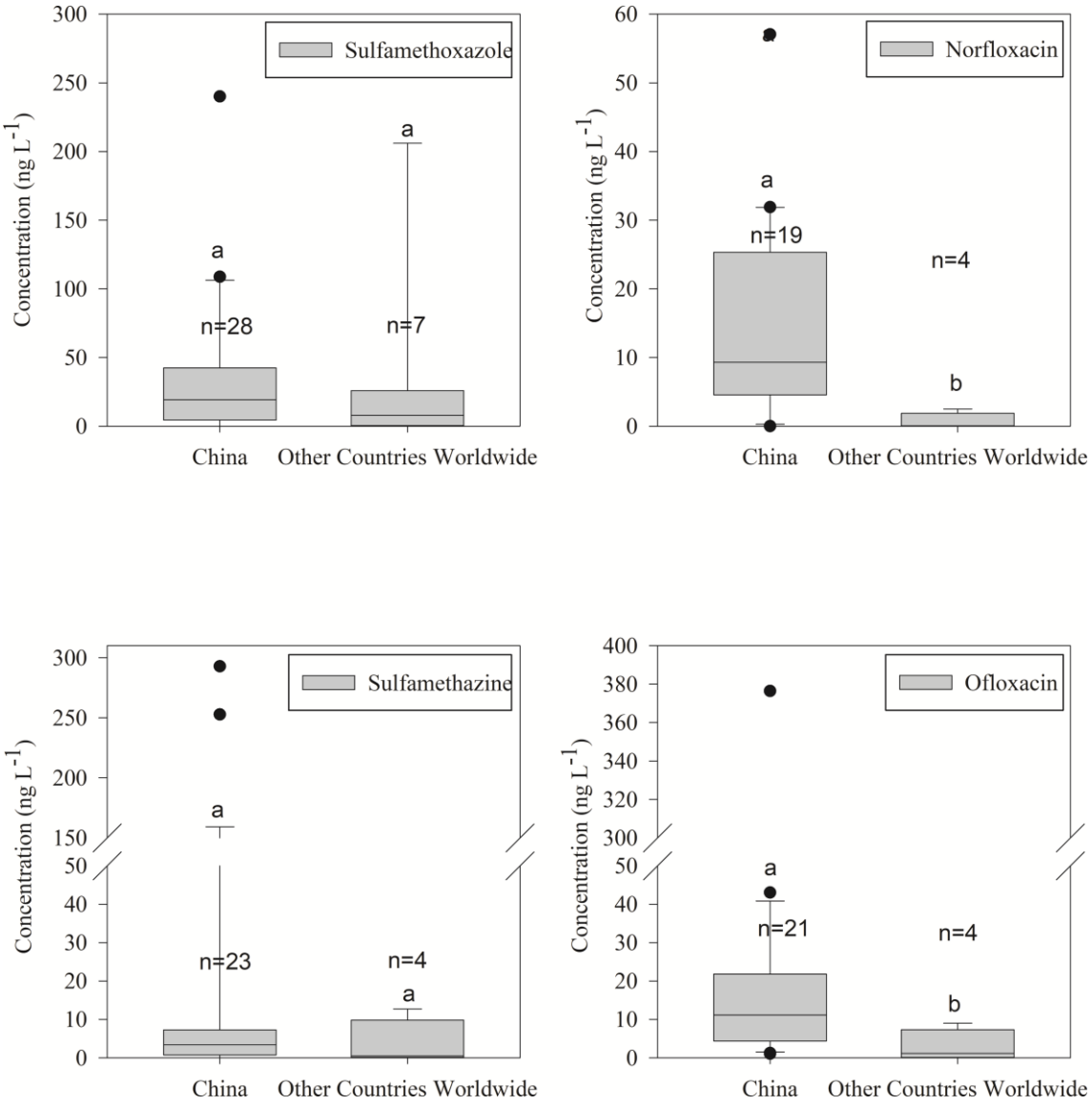
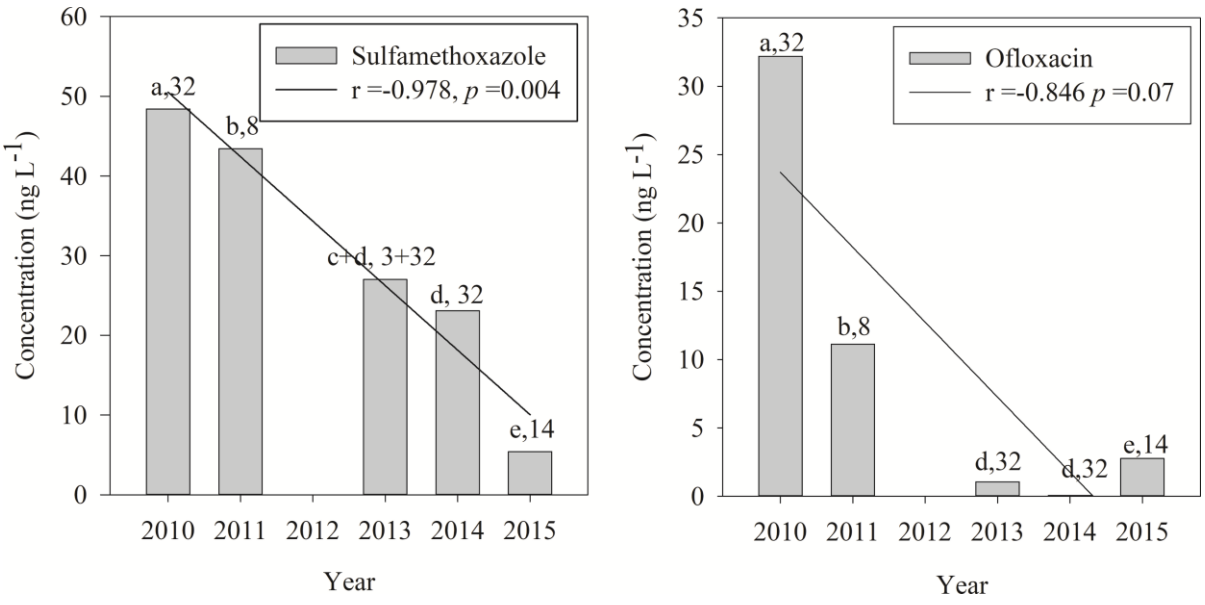

Sulfamethoxazole
Concentration (ng L-1)
300
250
200
150
100
50
0
a
a
n=28
n=7
China
Other Countries Worldwide
Norfloxacin
60
50
40
30
20
10
0
a
n=19
n=4
b
China
Other Countries Worldwide
Sulfamethazine
300
250
200
150
50
40
30
20
10
0
a
n=23
n=4
a
China
Other Countries Worldwide
Ofloxacin
400
380
360
340
320
300
50
40
30
20
10
0
a
n=21
n=4
b
China
Other Countries Worldwide

Fig. 3



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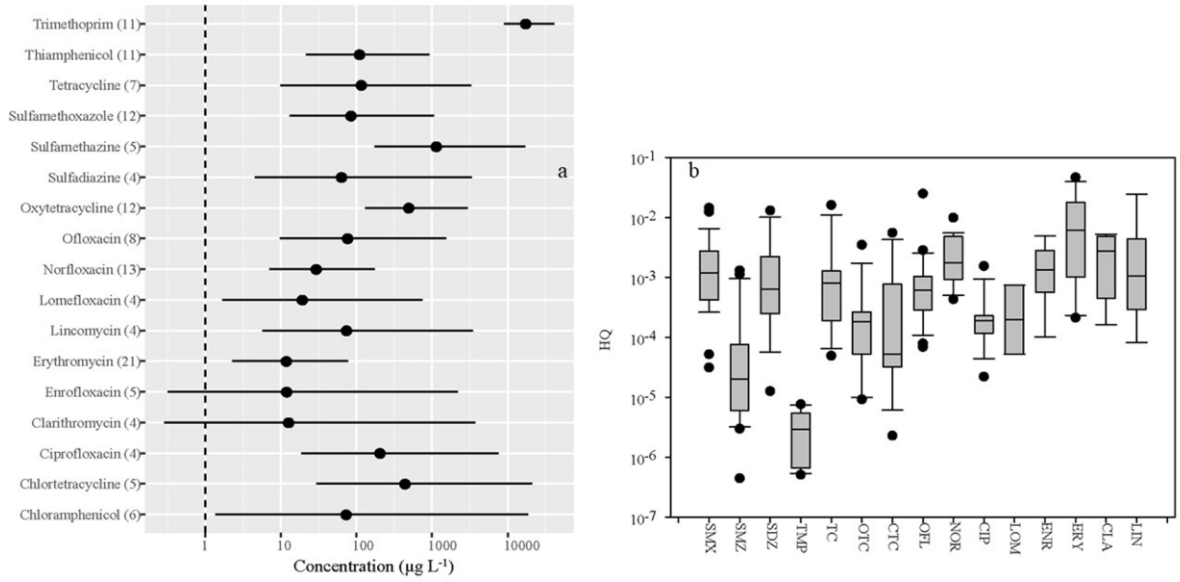
1343 **Fig. 4**



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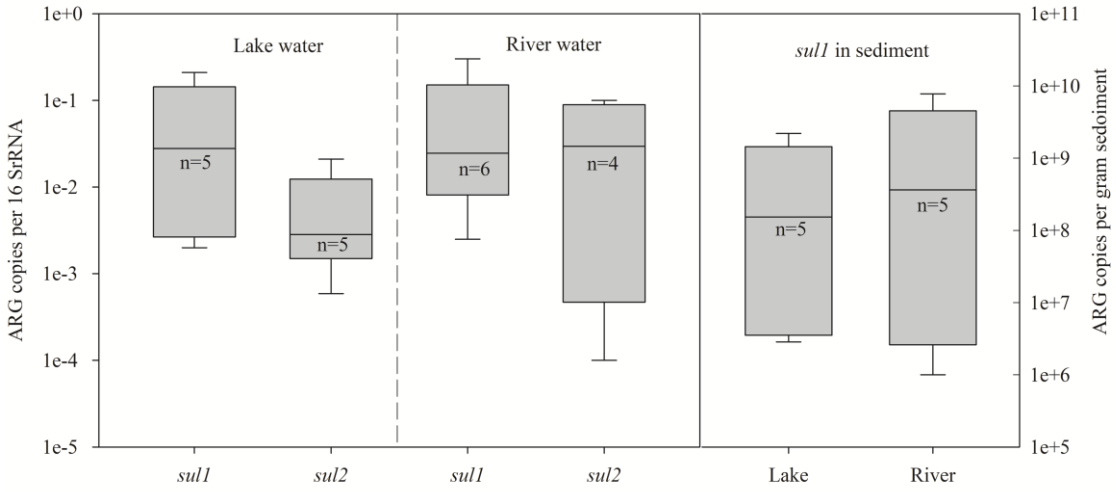
1345 **Fig. 5**



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1347 **Fig. 6**

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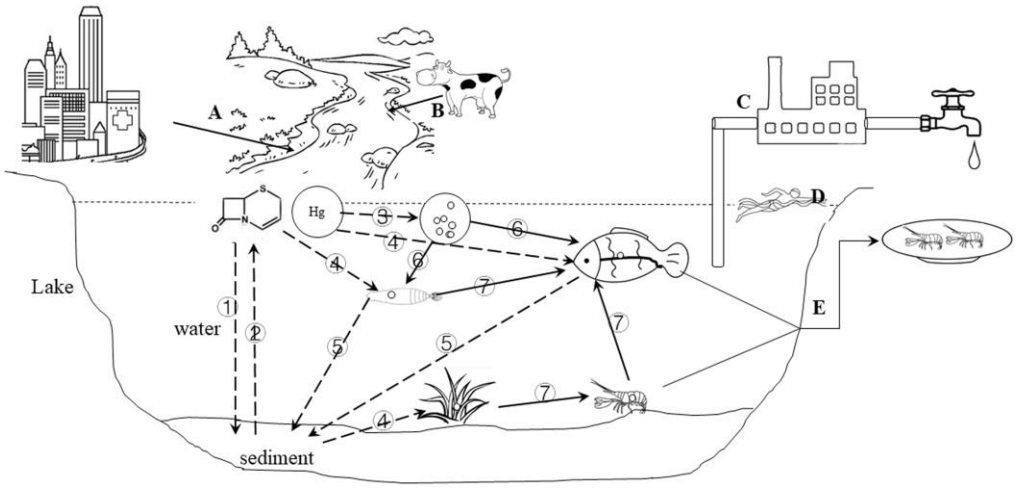

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1351 **Fig. 7**

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